REMARKS

Status of the Claims

The following claims are pending in the application: Claims 1, 3-5, and 17, 18, and 20-24. Claim 19 is canceled without prejudice or waiver.

Claim 18 Appears Not To Have Been Examined

Applicant respectfully points out that Claim 18 appears not to have been examined. In the Office Action Summary under Disposition of Claims, page 1, the PTO rejects Claim 18. However, Claim 18 is not included in any of the rejections in the Detailed Action on pages 2-12.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 5 and 19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

A. According to the PTO, Claim 5 is improper "since it is drawn to a compound that is a chemical molecule. In chemistry, compounds requisitely contain two or more elements. The instant Claim 5 fails to provide two or more elements. The recitation of a single chemical element or chemical molecule renders claim 5 indefinite." Office Action, page 2, item 4A (Emphasis added). Respectfully, this rejection is traversed.

Regarding the words chemical element and molecule, Applicant, being his own lexicographer, in the specification defined the term "compound" as follows:

> The term "compound" includes both the singular and the plural, and includes any single entity or combined entities that have activity that can be measured in the assays of the present invention. Such entities include, but are not limited to, chemical elements, molecules, compounds, mixtures, emulsions, chemotherapeutic agents, pharmacological agents, hormones, antibodies, growth factors, cellular factors, nucleic acids, proteins, peptides, peptidomimetics, nucleotides, carbohydrates, and combinations, fragments, analogs or derivatives of such entities. Specification, page 7, lines 12-19 (Emphasis added).

It is well established that applicants can be their own lexicographers and define the terms as they deem appropriate. With respect to the instant application, Applicant defined the term "compound" to include a "single chemical element" and a "chemical molecule," among other entities, in sharp contrast to the assertions of the PTO. Thus, because the term "compound" is defined by the Applicant to include a single chemical element and a chemical molecule, Claim 5 is definite. Accordingly, Applicant respectfully requests that the rejection of Claim 5 under 35 U.S.C. § 112, second paragraph, be withdrawn.

B. Claim 19 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claim 19 is canceled, thereby obviating this rejection. Accordingly, Applicant respectfully requests that the rejection of Claim 19 be withdrawn.

The Rejection Under 35 U.S.C. § 112, First Paragraph

Claim 1, 3-5, and 17-24 are rejected under 35 U.S.C. § 112, first paragraph, as failing to enable one of skill in the art to make and use the invention.

A. According to the PTO, the specification does not reasonably provide enablement for a method comprising measuring "any HSPG". Office Action, item 6 on pages 2-3. Specifically, the PTO asserts, "[t]he specification fails to teach how to measure the amount of either syndecan or glypican in cell culture. Neither does the specification teach how to discriminate between p[er]lecan, syndecan or glypican when measuring the amount of HSPGs." Office Action, page 3, lines 11-16. Further, the PTO states, "claim 1(b) recites measuring the amount of a HSPG in the first cell culture, not the amount of a HSPG in said cells. Since measuring mRNA expression requires isolating the mRNA from said cells. No mRNA is secreted by the cells to the cell culture for one skilled in the art to perform mRNA expression profile of the PGs." Office Action, page 4, lines 1-4.

Applicant maintains that the claims are fully enabled by the specification for reasons of record (*e.g.*, as previously given in Applicant's response mailed December 12, 2005). Further it is well known in the art that, at the very least, cell culture includes cells and media. Further, measuring mRNA levels is well known in the art as indicated in the references of record. Thus,

one of ordinary skill in the art would recognize that measuring mRNA in the cell culture includes measuring mRNA in cells.

Accordingly, Applicant maintains that the claimed invention is fully enabled, therefore, withdrawal of this rejection is respectfully requested.

B. The PTO maintains its rejection of Claim 5 for essentially the same reasons as set forth in the previous Office Action dated May 12, 2005. More specifically, the PTO states, "the specification does not provide guidance [to] the skilled artisan as to what molecules to be screened." Office Action page 3, lines 11-12. According to the PTO, "the specification fails to provide [] chemical and physical properties of **the claimed molecule**." Office Action page 3, lines 11-12.

For reasons of record (e.g., as previously stated in Applicant's response to the previous Office Action mailed May 15, 2005), it appears that Applicant and the PTO differ on what is being presently claimed. Applicant respectfully maintains that **the claimed invention is to a method** for detecting a compound, **not the actual compound** itself. Further, Applicant specifically states in Claim 1, from which Claim 5 depends, "adding the compound to a first cell culture, the compound comprising unknown cellular proliferative activity." (Emphasis added.) Thus, the compound is defined. Applicant is not claiming the compound or "molecule" comprising unknown cellular proliferative activity as asserted by the PTO, but rather a method of detecting a compound that affects cell proliferation. Accordingly, Applicant respectfully asserts that this rejection is improper as to the claimed method and requests that this rejection be withdrawn.

The Rejection Under 35 U.S.C. § 102(b)

Claims 1, 5, 17, and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Paka *et al.* (abstract Nov. 2, 1999). Respectfully, this rejection is traversed.

Applicant notes that, regarding Paka *et al.* (abstract Nov. 2, 1999), it is the PTO's position that, "[t]he claimed invention differs from the reference teachings only by the recitation that the HSPG is perlecan or syndecan in claims 3-4 and 22-23." Office Action, page 9, item 13, lines 4-5. Further, it is the PTO's position that, "[t]he claimed invention differs from the

reference teachings only by the recitation that the HSPG is glypican in claims 3 and 24." Office Action, page 8, item 12, lines 4-5. Yet, despite these assertions, the PTO maintains the rejection under 102(b).

The PTO states, "Paka *et al.* concluded that the ability of apoE isoforms to [1)] inhibit SMC proliferation **correlated** with [2)] their ability to stimulate perlecan production ..." Office Action, page 4, item 8, lines 16-17. (Emphasis added.) Again, the PTO states, "Paka *et al* concluded that the ability of apoE isoforms to [1)] inhibit SMC proliferation **correlated** with their [2)] ability to stimulate perlecan production ..." Office Action, page 5, lines 6-8. (Emphasis added.)

Further, according to the PTO, adding apoE to proliferating SMC "**inhibited** bFGF/EGF stimulated **(^{3}H)thymidine incorporation** into DNA by 50%." Office Action, page 4, item 8, lines 11-12. (Emphasis added.) But regarding HSPG levels, the PTO notes, apoE "increased $^{35}SO_4$ incorporation into cells" and "the HSPG increase was in perlecan." Office Action, page 4, item 8, lines 7-9, 11-12, and 15.

To establish a *prima facie* case of anticipation "the reference must teach each and every element of the claim." MPEP §2131. *Prima facie* anticipation in the present case is negated. With respect to the step of determining the affect of a lipoprotein (i.e., apoE) on proliferation, Paka *et al.* (abstract Nov. 2, 1999) measures **(^{3}H)thymidine incorporation**. In sharp contrast, the rejected claims recite measuring **HSPG** to determine the affect of a compound on proliferation. Even though Paka *et al.* measure proliferation and HSPG, HSPG are not measured to determine the affect of apoE on proliferation *per se*. To help illustrate Applicant's claimed screening method as compared to the method disclosed by Paka *et al.* (abstract Nov. 2, 1999), an element by element comparison is made below:

Paka *et al.*: A method for detecting apoE's affect on smooth muscle cell proliferation:
Claim 1: A method for detecting a compound that affects cell proliferation:

Paka *et al.*: i) adding apoE (known anti-proliferative) to a first SMC culture;
Claim 1: i) adding the compound (of unknown proliferative affect) to a first cell culture;

Paka *et al.*: ii) measuring amount of radioactivity incorporated into the DNA of the first SMC culture [or measuring number of cells of the first culture]; and
Claim 1: ii) measuring amount of HSPG in the first cell culture; and

Paka *et al.*: iii) comparing amount of radioactivity of the first SMC culture to the amount of radioactivity in a second culture not treated with apoE [or comparing amount of number of cells in the first culture to amount of cells in a second culture not treated with apoE];
Claim 1: iii) comparing amount of HSPG in the first culture to amount of the HSPG in a second culture not treated with the compound;

Paka *et al.*: wherein an increase or decrease in radioactivity [or cell number] indicates stimulation or inhibition of proliferation, respectively.
Claim 1: wherein an increase or decrease in the amount of HSPG indicates that the compound affects cell proliferation.

Thus, there is no teaching or suggestion anywhere in Paka *et al.* (abstract Nov. 2, 1999) for a screening method for detecting a compound that affects cell proliferation by measuring the amount of HSPG or perlecan production. Nowhere does Paka *et al.* (abstract Nov. 2, 1999) detect a compound that affects proliferation by measuring HSPG or perlecan production as an indicator of such an affect. Although Paka *et al.* (abstract Nov. 2, 1999) measures the amount of HSPG or perlecan production following exposure of cells to apoE, this measurement is not performed to determine whether apoE affects proliferation. To determine whether apoE affects proliferation, the amount of radioactivity incorporated into DNA (or the amount of cells) is determined following exposure to apoE.

Accordingly, Paka *et al.* (abstract Nov. 2, 1999) does not teach each and every element of the **claimed invention**. Withdrawal of the present rejection is respectfully requested in light of the remarks above.

The Rejection Under 35 U.S.C. § 102(b)

Claims 1, 5, 17, and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22). Respectfully, this rejection is traversed.

Applicant notes that, regarding Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22), it is the PTO's position that, "[t]he claimed invention differs from the reference teachings only by the recitation of compound comprising unknown cellular proliferative activity in claims 1 and 22-

24." Office Action, page 7, item 11, lines 22-23. Further, it is the PTO's position that, "[t]he claimed invention differs from the reference teachings only by the recitation that the HSPG is glypican in claims 3 and 24." Office Action, page 11, item 14, lines 5-6. Yet, despite these assertions, the PTO maintains its rejection under 102(b).

The PTO states, "[c]ontrary to [A]pplicant[s] assertion[,] Paka [*et al.* (JBC, Dec. 1999, IDS Ref. No. 22] teaches methods of detecting compounds that affect cell proliferation ... by measuring and comparing the amount of HSPG to indicate cell proliferation." Office Action, page 6, lines 17-20; emphasis added.

Applicant restates the discussion above as it relates to Paka *et al.* (abstract Nov. 2, 1999).

Further, Applicant respectfully disagrees with the PTO's above contention. Contrary to the PTO's assertion, Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) measures and compares the amount of HSPG **to indicate HSPG levels**.

To establish a *prima facie* case of anticipation "the reference must teach each and every element of the claim." MPEP §2131. *Prima facie* anticipation in the present case is negated. With respect to the step of determining the affect of a lipoprotein (i.e., apoE) on proliferation, Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) measures **(^{3}H)thymidine incorporation**. In sharp contrast, the rejected claims recite measuring **HSPG** to determine the affect of a compound on proliferation. Even though Paka *et al.* measure proliferation and HSPG, HSPG are not measured to determine the affect of apoE on proliferation *per se*. To help illustrate Applicant's claimed screening method as compared to the method disclosed by Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22), an element by element comparison is made below:

Paka *et al.*: A method for detecting apoE's affect on smooth muscle cell proliferation:
Claim 1: A method for detecting a compound that affects cell proliferation:

Paka *et al.*: i) adding apoE (known anti-proliferative) to a first SMC culture;
Claim 1: i) adding the compound (of unknown proliferative affect) to a first cell culture;

Paka *et al.*: ii) measuring amount of radioactivity incorporated into the DNA of the first SMC culture [or measuring number of cells of the first culture]; and
Claim 1: ii) measuring amount of HSPG in the first cell culture; and

Paka *et al.*: iii) comparing amount of radioactivity of the first SMC culture to the amount of radioactivity in a second culture not treated with apoE [or comparing amount of number of cells in the first culture to amount of cells in a second culture not treated with apoE];
Claim 1: iii) comparing amount of HSPG in the first culture to amount of the HSPG in a second culture not treated with the compound;

Paka *et al.*: wherein an increase or decrease in radioactivity [or cell number] indicates stimulation or inhibition of proliferation, respectively.
Claim 1: wherein an increase or decrease in the amount of HSPG indicates that the compound affects cell proliferation.

Thus, there is no teaching or suggestion anywhere in Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) for a screening method for detecting a compound that affects cell proliferation by measuring the amount of HSPG or perlecan production. Nowhere does Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) detect a compound that affects proliferation by measuring HSPG or perlecan production as an indicator of such an affect. Although Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) measures the amount of HSPG or perlecan production following exposure of cells to apoE, this measurement is not performed to determine whether apoE affects proliferation. To determine whether apoE affects proliferation, the amount of radioactivity incorporated into DNA (or the amount of cells) is determined following exposure to apoE.

Accordingly, Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) does not teach each and every element of the **claimed** invention. Withdrawal of the present rejection is respectfully requested in light of the remarks above.

The Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3-5, 17, 19 and 22 are rejected under 35 USC 103(a) as being unpatentable over Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) in view of Lee (2000). Respectfully, this rejection is traversed.

The PTO admits that "[t]he claimed invention differs from the reference [Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22] only by the recitation of compound comprising unknown cellular proliferative activity in claims 1 and 22-24." Office Action, page 7, lines 22-23. However, the PTO states, "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antiproliferative ApoE compound taught by Paka

[*et al.* (JBC, Dec. 1999, IDS Ref. No. 22)] with the compounds taught by Lee in a method for detecting a compound that affects cell proliferation taught by Paka [*et al.* (JBC, Dec. 1999, IDS Ref. No. 22)]. According to the PTO, "Lee teaches methods of identification of the endothelial compounds that regulates vascular response to injury in a crucial step toward elucidating the cellular and molecular mechanism underlying restenosis []." Office Action, page 7, last two lines and page 8, line 1.

To establish a *prima facie* case of obviousness, a reference (or references when combined) must teach or suggest all the claim limitations. MPEP §2143. *Prima facie* obviousness in the present instance is negated because the reference (or references when combined) do not teach or suggest all the claim limitations.

Notwithstanding the PTO's admission that "the claimed invention differs from Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) only by the recitation of a compound comprising unknown cellular proliferative activity," Applicant restates the discussion above as it relates to this reference.

Lee proposes a method for identifying endothelial-derived compounds, other than HSPG, that regulate the vascular response to injury. Lee, page 174, left column, Specific Aims section, first paragraph and page 177, left column, Proposal section, first sentence. Lee proposes that "experiments will be carried out using a coculture system, in which SMC are grown in the presence of tissue-engineered endothelial cells (Figure 6)." Lee, page 177, right column, Research Design and Methods section, Experimental System subsection, lines 1-4. Regarding determining the affect of a condition on SMC **proliferation** via endothelial-derived secretions, Lee proposes that the smooth muscle "**cells will be counted using a Coulter counter**." Lee, page 178, left column, Research Design and Methods section, SMC Growth Assay subsection, last line.; Emphasis added.

Thus, neither Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) nor Lee, individually or when combined, teach Applicant's claimed invention comprising **determining proliferation by measuring HSPG**. Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) **determines proliferation by measuring incorporation of radioactivity** whereas Lee proposes **determining proliferation by counting cells**.

Absent a teaching of all the claimed limitations, a *prima facie* case of obviousness against the claims cannot therefore be sustained, and withdrawal of the present ground of rejection is respectfully requested.

Moreover, *Prima facie* obviousness in the present instance is also negated by lack of any suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify reference teachings. Further, for reasons of record (*e.g.*, as previously stated in Applicant's response to the previous Office Action mailed May 15, 2005), not only does Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) at least lack suggestion or motivation to modify its teaching for a method to screen for compounds that affect proliferation by measuring HSPG instead of radioactivity or cell number, the reference appears to teach away from such a modification.

Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) itself suggests that its teaching may not extend beyond the specific affects of ApoE on smooth muscle cell a) proliferation and b) HSPG or perlecan production. Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) postulates that "because other growth modulators also regulate perlecan expression, this may be a key pathway in the regulation of SMC growth". Further, the reference states, "[w]e postulate that modulation of perlecan is a key step regulating SMC growth. Factors that increase perlecan inhibit cell growth, whereas those that decrease perlecan stimulate cell growth."

Elsewhere, Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) suggests that the observed correlation between a decrease in smooth cell proliferation and an increase in perlecan production may be specific to ApoE and smooth muscle cells. For example:

i) On page 36403, column 1, lines 19-20, the reference states, "ApoE did not inhibit proliferation of endothelial cells."

ii) On page 36407, column 1, lines 10-12, the reference states, "Cell surface HSPGs are required for the mitogenic activity of several growth factors (12) and thus are unlikely to inhibit cell growth."

iii) On page 36407, column 1, lines 20-23, the reference states, "In certain cell types, however, blocking perlecan production via antisense DNA inhibited cell growth (32-34)." citing Aviezer *et al.*, Mol. Cell. Biol. 17: pp1938-1946 (1997); Adatia *et al.*, Ann. Oncol. 8: pp1257-1361 (1997); and Sharma *et al.*, J. Clin. Invest. 102: 1599-1608 (1998).

iv) On page 36407, column 1, lines 32-33, the reference states, "Alternatively, perlecan produced by ApoE-stimulated cells is different."

v) On page 36407, column 2, lines, the reference states, "when added during the seeding of SMC's, perlecan antibody inhibited SMC growth by > 40% (not shown)."

As pointed out in 4(e)(iii) above, several references cited by Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) also suggest that the results of Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) may not extend beyond the specific affects of ApoE on smooth muscle cell a) proliferation and b) HSPG or perlecan production. These references are briefly discussed below.

According to Aviezer *et al.*, perlecan is abundant in proliferating cells and is capable of inducing basic fibroblast growth factor (bFGF)-receptor interactions *in vitro* and angiogenesis *in vivo*. Further, according to the reference, specific reduction of perlecan levels in mouse NIH 3T3 fibroblasts and human metastatic melanoma cells results in attenuated ability of bFGF to induce mitogenic activity. Thus, unlike the findings of Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) where an increase in perlecan is associated with the antiproliferative affect of apoE on smooth muscle cells, Aviezer *et al.* describe perlecan as associated with proliferative effects in cell types other than smooth muscle cells.

Sharma *et al.* blocked perlecan expression using antisense technology and showed that growth of colon carcinoma cells was markedly attenuated upon obliteration of perlecan gene expression and these effects correlated with reduced responsiveness to and affinity for mitogenic keratinocyte growth factor (FGF-7). Further, Sharma *et al.* showed that exogenous perlecan effectively reconstituted the activity of FGF-7 in the perlecan-deficient cells. Thus, unlike the findings of Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) where perlecan is associated with the antiproliferative affect of apoE on smooth muscle cells, according to Sharma *et al.*, perlecan is a potent inducer of tumor growth and angiogenesis.

Adatia *et al.* transfects malignant melanoma cells with a perlecan antisense cDNA construct and tested the *in vitro* behavior of the selected clones. Adatia *et al.* shows that the expression of antisense mRNA corresponds to a reduction of perlecan synthesis. In contrast to Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22), where reduced perlecan is associated with up-regulation of proliferation, in Adatia *et al.*, the cells with reduced perlecan synthesis show a down-regulation of proliferation and invasion.

For reasons stated above, Lee proposes a coculture system where "**cells will be counted using a Coulter counter**." Lee, page 178, left column, Research Design and Methods section, SMC Growth Assay subsection, last line. (Emphasis added.) Lee (2000) does not teach or suggest Applicant's claimed method for detecting a compound that affects proliferation comprising **determining proliferation by measuring HSPG**.

Absent any suggestion or motivation to combine or modify Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) or Lee (2000), a *prima facie* case of obviousness against the claims cannot be sustained, and withdrawal of the present ground of rejection is respectfully requested.

The Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3, and 24 are rejected under 35 USC 103(a) as being unpatentable over Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) in view of Lee (2000) and U.S. Patent No. 6,306,613 (the '613 patent). Respectfully, this rejection is traversed.

According to the PTO, "[t]he teachings of Paka et al. (Nov. 1999) and Lee article have been discussed, supra." Office Action, page 8, item 12, line 3; Emphasis added.

It is Applicant's understanding that the PTO intended Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) and not Paka et al. (Nov. 1999). If Applicant's understanding is incorrect, clarification is respectfully requested.

According to the PTO, "[t]he '613 patent teaches that K-glypican is part of a growing family of cell surface heparin sulfate proteoglycans (HSPGs) that play a role in regulating cellular proliferation, differentiation, and migration." Office Action, page 11, item 14, lines 7-9. The PTO asserts, "glypican plays a role in regulating cellular proliferation as taught by the '613 patent." Office Action, page 11, item 14, lines 17-18. Thus, according to the PTO, given that glypican plays a role in regulating cellular proliferation, it would have been obvious to one of ordinary skill is the art at the time the invention was made to measure the amount of glypican as taught by the '613 patent in determining cell proliferation as taught by the '613 patent." Office Action, page 11, item 14, lines 12-15.

To establish a *prima facie* case of obviousness, a reference (or references when combined) must teach or suggest all the claim limitations. MPEP §2143. *Prima facie*

obviousness in the present instance is negated because the reference (or references when combined) do not teach or suggest all the claim limitations.

Applicant restates the discussions above as they relate to Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) and Lee (2000).

The '613 patent discloses a method for identifying and using modulators of leaderless protein export. See '613, U.S. Patent No. 6,306,613, Title. According to '613, modulation of export can be achieved by altering binding of the leaderless protein and a transport molecule such as K-glypican. '613, U.S. Patent No. 6,306,613, Abstract, lines 1-12; See also column 15, lines 18-35. Nowhere, does '613 either disclose or suggest the use of HSPG, or specifically a glypican, in a method for detecting a compound that affects cell proliferation where proliferation is determined by measuring HSPG.

First, Applicant respectfully disagrees with the PTO's assertion that the '613 patent teaches that "glypican plays a role in regulating cellular proliferation." Office Action, page 11, item 14, lines 17-18. Just because the '613 patent may mention that K-glypican is part of a growing family of cell surface HSPGs that play a role in regulating cellular proliferation, it does not follow that the statement teaches or suggests that glypican <u>has</u> a role in regulating proliferation. See, for example, the '613 patent, column 15, lines 20-23.

Regardless, neither Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22), Lee (2000) nor the '613 patent, individually or in combination, teach Applicant's assay method for **<u>detecting a compound that affects proliferation by measuring HSPG</u>**. Paka et al. (JBC, Dec. 1999, IDS Ref. No. 22) **<u>determines proliferation by measuring incorporation of radioactivity</u>**. Lee (2000) **<u>proposes determining proliferation by counting cells</u>**. And, the '613 patent mentions **<u>determining proliferation by using incorporation of tritiated thymidine</u>** (see, for example, the '613 patent, column24, lines 53-56.

Thus, none of the references, individually or in combination, teach all the claimed limitations. Absent a teaching of all the claimed limitations, a *prima facie* case of obviousness against the claims cannot therefore be sustained, and withdrawal of the present ground of rejection is respectfully requested.

The Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3-4, and 22-23 are rejected under 35 USC 103(a) as being unpatentable over Paka *et al.* (abstract Nov. 2, 1999) in view of Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22). Respectfully, this rejection is traversed.

To establish a *prima facie* case of obviousness, a reference (or references when combined) must teach or suggest all the claim limitations. MPEP §2143. *Prima facie* obviousness in the present instance is negated because the reference (or references when combined) do not teach or suggest all the claim limitations.

Applicant respectfully asserts that the disclosure of Paka *et al.* (abstract Nov. 2, 1999) is essentially redundant in view of the more detailed Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22). The Paka *et al.* (abstract Nov. 2, 1999) abstract is near verbatim to the abstract section of the Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) article. Moreover, both references have authors in common. Thus, Paka *et al.* (abstract Nov. 2, 1999) is essentially a summary of the results of experiments disclosed in more detail in Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22).

Applicant restates the discussions above as they relate to Paka *et al.* (abstract Nov. 2, 1999) and Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22). Further, as stated above, neither Paka *et al.* (abstract Nov. 2, 1999) nor Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22), individually or when combined, teach Applicant's **determining proliferation by measuring HSPG**. Both, Paka et al. (abstract Nov. 2, 1999) and Paka et al. (JBC, Dec. 1999, IDS Ref. No. 22) **determine proliferation by measuring incorporation of radioactivity or by counting cells**. Absent a teaching of all the claimed limitations, a *prima facie* case of obviousness against the claims cannot therefore be sustained, and withdrawal of the present ground of rejection is respectfully requested.

The Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3, and 24 are rejected under 35 USC 103(a) as being unpatentable over Paka *et al.* (abstract Nov. 2, 1999) or Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) in view of U.S. Patent No. 6,306,613 (the '613 patent). Respectfully, this rejection is traversed.

The PTO states, "The teachings of Paka *et al.* [(abstract Nov. 2, 1999)] and Paka *et al.* [(JBC, Dec. 1999, IDS Ref. No. 22)] have been discussed, supra.

According to the PTO, "[t]he '613 patent teaches that K-glypican is part of a growing family of cell surface heparin sulfate proteoglycans (HSPGs) that play a role in regulating cellular proliferation, differentiation, and migration." Office Action, page 11, item 14, lines 7-9. The PTO asserts, "glypican plays a role in regulating cellular proliferation as taught by the '613 patent." Office Action, page 11, item 14, lines 17-18. Thus, according to the PTO, given that glypican plays a role in regulating cellular proliferation, it would have been obvious to one of ordinary skill is the art at the time the invention was made to measure the amount of glypican as taught by the '613 patent in determining cell proliferation as taught by the '613 patent." Office Action, page 11, item 14, lines 12-15.

To establish a *prima facie* case of obviousness, a reference (or references when combined) must teach or suggest all the claim limitations. MPEP §2143. *Prima facie* obviousness in the present instance is negated because the reference (or references when combined) do not teach or suggest all the claim limitations.

Applicant restates the discussions above as they relate to Paka *et al.* (abstract Nov. 2, 1999) and Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22).

The '613 patent discloses a method for identifying and using modulators of leaderless protein export. See the '613 patent, Title. According to '613, modulation of export can be achieved by altering binding of the leaderless protein and a transport molecule such as K-glypican. The '613 patent, Abstract, lines 1-12 and column 15, lines 18-35. Nowhere, does the '613 patent either disclose or suggest the use of HSPG, or specifically a glypican, in a method for detecting a compound that affects cell proliferation where proliferation is determined by measuring HSPG.

First, Applicant's respectfully disagree with the PTO's assertion that the '613 patent teaches that "glypican plays a role in regulating cellular proliferation as taught by the '613 patent." Office Action, page 11, item 14, lines 17-18. Just because the '613 patent may mention that K-glypican is part of a growing family of cell surface HSPGs that play a role in regulating cellular proliferation, it does not follow that the statement teaches or suggests that glypican <u>has</u> a role in regulating proliferation. See, for example, the '613 patent, column 15, lines 20-23.

Regardless, neither Paka *et al.* (abstract Nov. 2, 1999), Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) nor the '613 patent, individually or when combined, teach Applicant's assay method

for **detecting a compound that affects proliferation by measuring HSPG.** Both Paka *et al.* (abstract Nov. 2, 1999) and Paka *et al.* (JBC, Dec. 1999, IDS Ref. No. 22) **determine proliferation by measuring incorporation of radioactivity or by counting cells.** And ,the '613 patent proposes **determining proliferation, if at all, by using incorporation of tritiated thymidine** (see, for example, the '613 patent, column24, lines 53-56). Thus, none of the references alone or in combination teach all the limitations of the claimed invention.

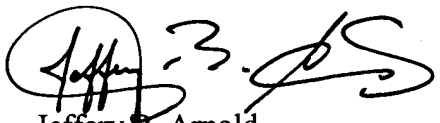
Absent a teaching of all the claimed limitations, a *prima facie* case of obviousness against the claims cannot therefore be sustained, and withdrawal of the present ground of rejection is respectfully requested.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully assert that the rejection of the claims as set forth in the final Office Action of March 10, 2006 have been addressed and overcome. Applicants further respectfully assert that all claims are in condition for allowance and request that a Notice of Allowance be issued. If issues may be resolved through PTO's Amendment, or clarified in any manner, a call to the undersigned attorney at (404) 879-2433 is courteously solicited.

The Commissioner is hereby authorized to charge any fees due, or credit any overpayment, to Deposit Account No. 09-0528.

Respectfully submitted,



Date: August 10, 2006

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